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Applicants: Juin-Jet Hwang et al.

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For : ULTRASONIC DIAGNOSTIC IMAGING WITH HARMONIC CONTRAST AGENTS

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INFORMATION DISCLOSURE STATEMENT

Dear Sir:

The Examiner has brought to applicants' attention US Pat. 6,506,158 (Kawagishi et al.) The paragraph beginning on line 28 of column 1 of that patent describes the pulse inversion method of extracting nonlinear components from a received ultrasonic echo signal, and refers to a technical report titled "Nonlinear Propagation of Ultrasonic Pulses" by Iwao Abiru and Tomoo Kamakura, published in 1989. Applicants' attorney has made a number of inquiries and has located a copy of this technical report in a library in Japan. Since the technical report was available only in Japanese, applicants' attorney had the technical report translated by the translations department of Philips Intellectual Property & Standards in Europe. A copy of the technical report and its

English translation are enclosed. Applicants' attorney and one of the inventors of the above-identified patent application have reviewed the Abiru et al. report and its translation, and offer the following comments.

For the convenience of the Examiner, a copy of the presently pending claims in this reissue application is attached in the Appendix at the end of this submission.

Abiru et al. present a mathematical model and experimental results on their studies of the non-linear propagation of ultrasonic wave pulses. Their work was confined to transmitted ultrasound waves as would be used in a through-transmission ultrasound system, where the transmitter transmits to a receiver and the subject of the study is located between the transmitter and the receiver. The present invention, on the other hand, is confined to pulse-echo ultrasound, where ultrasonic waves are transmitted to the subject, which returns echo signals that are received and processed to form an image.

The first part of the Abiru et al. report discusses a familiar mathematical model of the propagation characteristics of a transmitted ultrasound wave, the KZK (Khokhlov-Zabolotskaya-Kuznetsov) equation. The KZK equation is used by Abiru et al. to model a transmitted wave, not an echo signal. Reflection and scattering, the important characteristics of an echo signal for pulse-echo imaging, are not modeled, nor are they measured experimentally in the second part of the report.

After modeling the propagation of a transmitted wave, Abiru et al. conduct an experiment with a transmitted wave. The experimental setup is a through-transmission system located in a water tank in which an oscillator drives a 9.5 mm sound source and the waves propagating out from the sound source through the water are received by a 1 mm PVDF hydrophone located 5 cm to 20 cm away. The oscillator has a nominal transmit frequency of 2.3 MHz (4.55×10^{-7} sec.

periodicity) and transmits a wave with a sound pressure of about 1.7 atm (170 kiloPascals). The oscillator transmits two waves p+ and p- which were modeled mathematically in equations (27). The transmitted signals are received by the hydrophone and used in the calculation of formula (27) to separate out a primary wave p_1 and a secondary wave p_2. The spectral plot of Fig. 12 on page 60 of the report shows that the primary wave p_1 contains the odd order harmonics and the secondary wave p_2 contains the even order harmonics.

Abiru et al. do not discuss image formation at all and make no reference to pulse-echo measurements or backscatter imaging. They do not mention the use of more than two pulses. And there is no suggestion of contrast agents or harmonic contrast agents.

The non-linear propagation report of Abiru et al. would not suggest any applications in pulse-echo diagnostic imaging for at least two reasons: its use of water as the propagation medium and its use of direct transmission rather than pulse-echo. To appreciate this, reference is made to the enclosed pages of the Ph.D. thesis of Dr. Matthew R. Rielly which was published in the year 2000. Applicants would be happy to provide a full copy of the thesis should the Examiner desire to see it. Like Abiru et al., Dr. Rielly was doing both theoretical and experimental investigations of nonlinear propagation of ultrasound waves. Like Abiru et al., Dr. Rielly did analytical modeling with the KZK formula. His experimental setup is seen to be very similar to that used by Abiru et al. as illustrated in Figure 6.1 of his thesis on page 85. The setup is a water tank with a 2.25 MHz transmitter at one end and a PVDF hydrophone at the other. But unlike Abiru et al., Dr. Rielly considered the attenuation of tissue. For this purpose Dr. Rielly conducted a number of experiments with a tissue mimicking fluid which mirrored the attenuative effect of tissue. As is well known, the

attenuation coefficient of water is 0.00217 $dBcm^{-1}MHz^{-m}$. The characteristics of Dr. Rielly's soft tissue mimicking fluid are listed in Fig. 7.17 of the thesis on page 118, which show an attenuation coefficient α_0 of 0.3 $dBcm^{-1}MHz^{-m}$, which is over one hundred and thirty times greater than that of water. Fig. 7.18 shows the published acoustic parameters for liver tissue, which compare favorably with that of the tissue mimicking fluid, including an attenuation coefficient α_0 of 0.4 dB* $cm^{-1}MHz^{-m}$.

Dr. Rielly performed a number of experiments with his water tank setup, the conditions of which are summarized in Fig. 8.1 on page 122. In his baseline experiment he repeated the water experiment of Abiru et al. using a transmit sound pressure of 135 kPa, comparable to the 170 kPa transmission pressure of Abiru et al. The transmitted ultrasound waves were focused at the hydrophone at a range of 18.2 cm, comparable to the 20 cm range of Abiru et al. Fig. 8.2 on page 123 illustrates the measurements made of the fundamental and subsequent three harmonics which show an amplified level at the focus of over 4 kPa for the second harmonic in water. This is the same strong response obtained by Abiru et al. due to the very low attenuation of water on the transmitted waves.

Dr. Rielly also performed an experiment with his soft tissue mimicking fluid as the propagation medium with a transmit sound pressure of 150 kPa and a focus of 15.6 cm. The measurements from this experiment are illustrated in Fig. 8.10 on page 127, which show a peak second harmonic response at the focus of less than one kPa with the same receive gain. The higher order harmonics are virtually at the noise level. It is seen that a significantly lesser response is obtained when the transmitted waves experience the attenuative effects of tissue. In the next experiment Dr. Rielly doubled his transmit sound pressure to 310 kPa. The measurements of this experiment, illustrated in Fig. 8.12, show that the peak

second harmonic level is at an amplified level of 2 kPa, still half that obtained with water at half the transmit pressure.

Like Abiru et al., Dr. Rielly did not do any imaging in his work. The maximum sound pressure used in his experiments, 310 kPa, is far below the levels needed to make a clinically acceptable diagnostic image. Today's commercial ultrasound systems which are used for harmonic imaging transmit at a significantly higher sound pressure level than is found in any of these experiments. For instance, the C5-1 probe used for 2D harmonic imaging modes on Philips ultrasound systems transmits at a sound pressure of 1.0-1.2 megaPascals (megaPa). This all illustrates that water experiments done by Abiru et al. do not commend themselves to anyone trying to do harmonic imaging in tissue.

The other significant fact of the Abiru et al. report is that it was, like the experiments done by Dr. Rielly, a study of the direct reception of a transmitted wave and did not extend to pulse-echo reception. Abiru et al. modeled with the KZK formula for a propagating transmit wave, and performed their experiment by receiving a transmit wave. As is well known, the levels of echoes received in pulse-echo ultrasound are 40-60 dB down from the transmit levels, and harmonic levels are at least another 6 dB down from the fundamental echo component. Thus, only a tiny fraction of the transmitted signal energy is received for imaging. It should be remembered that Abiru et al. were doing their experiments in 1989 before results of harmonic contrast imaging were first published in the 1990's and before the invention of tissue harmonic imaging in 1996. These factors all demonstrate that nonlinear propagation experiments with directly transmitted ultrasound do not commend themselves to one skilled in the art who is facing the challenge of producing a harmonic diagnostic ultrasound image with pulse-echo ultrasound.

Returning to the Kawagishi et al. patent found by the Examiner, the authors of this patent are making the point that both Abiru et al. and they are making use of the common physical phenomenon that harmonic components are generated in proportion to the square of a fundamental wave. And with the 20:20 hindsight benefit of the knowledge of contrast imaging and tissue harmonic imaging that was available to them in the year 2000, the authors are in a position to analogize the transmit wave extraction technique used by Abiru et al. to the later invention of pulse inversion for diagnostic imaging.

Turning to the pending claims, it is seen that all of them are directed to pulse-echo ultrasound and not through-transmission ultrasound. Claim 1, for example has steps of transmitting first and second ultrasonic pulses to a contrast agent and detecting the harmonic responses from the agent. As previously mentioned, Abiru et al. do not show or suggest any application for contrast agents. Claims 5, 14, 17 and 20 claim a method involving the transmission and reception of echoes from at least three ultrasonic pulses. Abiru et al. do not show or suggest the use of anything but two transmissions. For these further reasons it is respectfully submitted that the pending claims are patentable over Abiru et al. either alone or in combination with other references.

Since the previously cited references have been shown to be of ineffective dates, it is respectfully submitted that this application is now in condition for allowance. Favorable reconsideration is respectfully requested.

Respectfully submitted,

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APPENDIX: PENDING CLAIMS AS OF DECEMBER 12, 2007

1. (original) A method of ultrasonically detecting the ultrasonic response of an ultrasonic contrast agent comprising the steps of: transmitting a first ultrasonic pulse to said ultrasonic contrast agent to cause a first harmonic response;

transmitting a second ultrasonic pulse of a different polarity than said first ultrasonic pulse to said harmonic contrast agent to cause a second harmonic response;

detecting said first and second harmonic responses; and

combining said first and second harmonic responses.

2. (original) The method of claim 1, wherein said step of combining comprises summing said first and second harmonic responses.

3. (original) The method of claim 1, wherein said step of combining comprises integrating said first and second harmonic responses.

4. (original) The method of claim 1, wherein said transmitting step comprises transmitting pulses which exhibit a pulse energy which is within a range which causes microbubbles of said ultrasonic contrast agent to oscillate without substantial microbubble destruction.

5. (original) A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

transmitting at least three ultrasonic pulses into the body which exhibit first and second characteristics that cause a reduction in the linear echo response when echoes received in response to such pulses are combined;

receiving echoes in response to said ultrasonic pulses; and

combining said echoes to produce a nonlinear response.

6. (original) The method of Claim 5, wherein said step of receiving echoes comprises receiving echoes from a given location in the body.

7. (original) The method of Claim 5, wherein said ultrasonic pulses are transmitted in a sequence in which said first and second characteristics are alternated from pulse to pulse.

8. (original) The method of Claim 5, wherein said step of combining comprises summing pairs of echoes.

9. (original) The method of Claim 5, wherein said ultrasonic pulses are transmitted in a sequence in which said first and second characteristics are alternated from pulse to pulse; and

wherein said step of combining comprises summing pairs of echoes from successive pulses.

10. (original) The method of Claim 5, wherein said first and second characteristics comprise first and second polarities.

11. (Previously presented) The method of Claim 10, wherein said transmitted ultrasonic pulses are of the form {p -p p ...}.

12. (Previously presented) The method of Claim 5, wherein said step of combining produces a sum result S which is substantially equal to $S = \sum_{j=1}^{n-1}(E_j + E_{j+1})$, where E_j and E_{j+1}

are pulse echoes.

13. (original) The method of Claim 12, wherein the number of ultrasonic pulses which is transmitted is three.

14. (original) A method of ultrasonically detecting the nonlinear ultrasonic response of a medium inside the body comprising the steps of:

transmitting a first ultrasonic pulse to said medium to cause a first echo response;

transmitting a second ultrasonic pulse to said medium to cause a second echo response;

transmitting a third ultrasonic pulse to said medium to cause a third echo response which is substantially the same as said first echo response; and

combining said first, second and third echo responses to produce a nonlinear response.

15. (Previously presented) The method of Claim 14, wherein said transmitted ultrasonic pulses are of the form {p -p p}.

16. (Previously presented) The method of Claim 14, wherein said step of combining produces a sum result S which is substantially equal to $S = \sum_{j=1}^{n-1}(E_j + E_{j+1})$, where E_j and E_{j+1} are pulse echoes.

17. (original) A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

transmitting at least three ultrasonic pulses into the body in a sequence which is of the form {p -p p -p ... -p p};

receiving echoes in response to said ultrasonic pulses which comprise a sequence of the form $\{E_1\ E_2\ E_3\ E_4\ \ldots\ E_{n-1}\ E_n\}$;

and

accumulating said echoes to produce a nonlinear response.

18. (original) The method of Claim 17, wherein said step of accumulating comprises accumulating pairs of consecutive echoes.

19. (Previously presented) The method of Claim 17, wherein said step of accumulating produces a sum result S which is substantially equal to $S = \sum_{j=1}^{n-1} (E_j + E_{j+1})$, where E_j and E_{j+1} are pulse echoes.

20. (original) A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

transmitting a sequence of at least three ultrasonic pulses into the body which exhibit a transmit characteristic which alternates from pulse to pulse;

receiving echoes in response to said ultrasonic pulses; and

combining said echoes to produce a nonlinear response.

21. (original) The method of Claim 20, wherein said pulses are transmitted to a given location in the body; and

wherein said step of combining reduces the primary component of said echoes and produces a harmonic response.

22. (original) The method of Claim 20, wherein said step of transmitting produces a sequence of echoes relating to a given location in the body in which the phase of the primary component of echoes produced by one transmit characteristic is out of phase with the phase of the primary component of echoes produced by the alternate transmit characteristic.

23. (original) The method of Claim 22, wherein said step of combining reduces the primary component of the combined echoes and produces a harmonic response.

24. (original) The method of Claim 23, wherein said transmit characteristic is a polarity differential from pulse to pulse.

25. (original) The method of Claim 23, wherein said transmit characteristic is a phase differential from pulse to pulse.